Does Better Glycemic Control of Known Diabetics During the Perioperative Period Reduce Postoperative Surgical Infections?

By

Kimberly Denise Clay

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INTRODUCTION

Research has shown that tight control of blood glucose can decrease or eliminate some long-term complications from Diabetes Mellitus (DM) (1, 2). Maintaining blood glucose levels under tight control has been addressed in the inpatient as well as in the outpatient setting (1, 2). If maintaining appropriate blood glucose levels on an outpatient basis diminishes complications, does tight control during the perioperative period prevent infectious complications as well?

It is this question, exclusively in the case of diabetic patients who are going through surgery, which will be the focus of this paper. Here, I will examine the evidence for glucose control as it relates to postoperative infections. I will see if sufficient evidence to make clinical recommendations is available. Groups [1]have published their recommendations and guidelines on perioperative glycemic control in diabetic patients (3, 4, and 5). Therefore, in the final section of this paper, I will critique recommendations made by various groups against this evidence base and make suggestions for future research in this area.

BACKGROUND ON DIABETES MELLITUS

Diabetes Mellitus (DM) is the most common endocrine disorder. It is subdivided into several different classifications that are based on insulin deficiency and insulin resistance. The two major classifications are Type 1 and Type 2. Type 1 DM is defined as beta cell destruction with a resultant lack of insulin production capacity. Type 2 DM is defined as insulin resistance with insulin deficiency.

The pathophysiology of Type 1 DM is well known; however, the pathophysiology of Type 2 DM is less clear. It is common knowledge that in Type 2 DM, organs that use insulin (primarily muscle and liver) are not able to take up glucose due to insulin resistance. This results in decreased uptake and storage of glucose in muscle and inappropriate hepatic glucose production (6). To compensate for high blood glucose levels, the body attempts to rectify the situation by increasing circulating insulin. However, in the presence of insulin resistance, glucose levels remain elevated. Increased circulating insulin causes an increased lipogenesis and an increase in fat stores thus helping to perpetuate a vicious cycle.

Some inciting factors for the development of Type 2 DM may include high circulating free fatty acids, cortisol and catecholamines (6). Additionally, there is a genetic aspect to this disease with a strong environmental influence on expression. Twin studies demonstrate a greater than 30 percent concordance among monozygotic twin pairs in the expression of Type 2 DM (6). Moreover, a sedentary lifestyle, high-fat diet and belonging to certain ethnic groups (e.g. African Americans, Native Americans and Hispanics) are also contributing factors to the development of DM.

Diabetes is a highly prevalent disease. The number of affected patients increases every year. The CDC reports approximately 4.2 percent of the adult U.S. population as having some form of diabetes. This represents approximately 15 million Americans, 90% of which suffer from Type 2 DM (7). Additionally, there are approximately 16-20 million with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), both of which are considered "prediabetes" (8).

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[1] The American Diabetes Association (ADA); the American Healthways Inc; Dr. Alex Stagnaro-Green

Type 1 DM is usually seen in young children or adults but can occur at any age. Type 2 DM can occur at any age, but incidence increases with age. The American Diabetes Association (ADA) reports that 8 up to 45 percent of children with newly diagnosed diabetes have Type 2 DM (9). This represents an increase from an estimated 8 percent in 1994 (9). This increase in prevalence is not limited to children and adolescents. The prevalence of diagnosed diabetes in U.S. adults increased from 4.9 percent in 1990 to 6.5 percent in 1998 (10).

Complications Associated with Diabetes

The American Diabetes Association (ADA) suggests that tight control of blood glucose is defined as a preprandial (fasting/premeal) plasma glucose of 90-130 mg/dL, a postprandial (postmeal) plasma glucose of 110 –170 mg/dL, and a bedtime glucose of 100 – 160 mg/dL (3). The Diabetes Control and Complications Trial (DCCT) and The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that patients whose blood glucose levels were kept within the recommended ranges on an outpatient basis had fewer complications from diabetes (1, 11). Blood glucose levels not kept in these recommended ranges resulted in patients developing more diabetic complications (1, 11).

Diabetic complications can be microvascular (e.g., nephropathy, neuropathy, and retinopathy) and/or macrovascular (e.g., cardiovascular or cerebrovascular disease). All of these complications can decrease both the quality and quantity of life for patients. However, studies indicate that one way to reduce a patient's risk of developing these complications is to intensively treat his or her diabetes (1, 11).

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive control of blood glucose reduced the risk of microvascular progression of retinopathy and nephropathy (1). The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that in Type 2 DM, tight glucose control prevented or delayed nephropathy, neuropathy and retinopathy (11). Additionally, the more normal a patient's HbA1c (a measure of the average glucose in a patient's blood over two or three months), the lower the patient's lipid levels. This combination decreased the patient's risk of developing Coronary Heart Disease (CHD) (11)[2].

Secondary to the many complications encountered by Type 2 DM patients, they in comparison to non-diabetics, have an increased likelihood of needing extensive and repeated inpatient medical care (12). The National Health and Nutrition Examination Survey (NHANES II), conducted from 1976 until 1980, showed that 29.9 percent of persons 65 and older with known diabetes, in comparison to non-diabetics, have been hospitalized for diabetes-related conditions and other medical reasons (12). The investigators estimated that hospitalizations were 1.7 times more common for elderly patients with diabetes than those without diabetes (12).

Cost Associated with Diabetes

Healthcare expenditures for people with diabetes are approximately 17 percent of all U.S. healthcare expenditures totaling approximately $105 billion dollars annually (7). Over 4 million people with diabetes are admitted to a hospital each year, and the number of admissions is increasing by 4.5 to 5.0 percent annually (4).

[2] CHD = fatal or non fatal MI, or angina with abnormal ECG.

Diabetic patients comprise 20 percent of all hospital admissions. Twenty-five percent of all hospital stays and nearly 25 percent of all hospital charges are attributed to diabetic patients (4). The current annual total hospital cost for people with diabetes exceeds $98 billion (11). Total inpatient resource consumption and length of stay for a diabetic patient are 30 to 40 percent more than that of hospitalized non-diabetic patient (4). Consequently, the morbidity and costs associated with diabetes have resulted in inpatient management strategies focused on improving outcomes and implementing cost-effective methodologies.

OBJECTIVES

It is known that tight glucose control on an outpatient basis over time has been shown to decrease long-term diabetic complications (1, 11). The paper will review published literature on perioperative infections relating to glucose control in diabetic surgical patients. The objective of this systematic review is to determine what, if any, effect glucose control has on the type, length and severity of infectious outcomes.

PRIMARY QUESTION:

Does better glycemic control reduce perioperative infections?

METHODS

Identification and Retrieval of Primary Studies

Search Strategy: Searches were conducted for studies that examined perioperative outcomes in diabetic surgical patients comprised by papers indexed by Medline from 1966 to 2003, the Cochrane Clinical Trials Registry (1st quarter 2003), and an evidence-based medicine database that included the Cochrane Database of Systematic Review (CDSR) (1st quarter 2003), the American College of Physicians (ACP) Journal Club (1st quarter 2003), and the Database of Abstracts of Reviews of Effectiveness (DARE) (1st quarter 2003). Reference lists of relevant review articles and included articles were screened for other, previously unidentified, studies. The search strategies were as follows:

Medline 1966 to 2003

#	Search History	Results
1	(diabetes and (surgery or surgical or operative)).mp. [mp=title, abstract, case registry/ec number word, mesh subject heading]	5925
2	Limit 1 to (human and English language)	2203
3	(glucose and control). mp. [mp=title, abstract, cas registry/ec number work, mesh subject heading]	38236
4	Limit 3 to (human and english language)	17772
5	2 and 4	180

Cochrane Clinical Trial Registry

#	Search History	Results
1	glucose control.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	288
2	diabetic patients.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	2068
3	surgical patients.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1058
4	1,3 and 4	103

CDSR, ACP Journal Club, DARE

#	Search History	Results
1	glucose control.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	45
2	diabetic patients.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	54
3	surgical patients.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	107
4	1,3 and 4	9

Inclusion Criteria

The following criteria were used for the inclusion of studies into the systematic review:

1. Study goals must have been primarily to find an association between blood glucose levels and perioperative infections.
2. Study must have specified the diabetic status of the patient population at the beginning of the study as well as the type of surgical procedure performed.
3. Study must have selected outcomes directly related to the operation performed and not to a previously known diagnosis.

4. Study must have reported serum blood glucose levels or HgA1c with respect to outcome measures.
5. Study must have included operations that required at least an overnight hospital admission.
6. Study must have used human subjects and have been published in English.

Exclusion Criteria

The following criteria were used to exclude papers from further consideration:

1. No comparison group or control group,
2. Retrospective study design, or
3. No information on inpatient glucose control.

Full text copies of all potentially relevant studies were obtained by reviewing abstracts from both electronic and manual searches. I manually searched the references of the electronically obtained abstracts that I included in the study to identify articles overlooked by the electronic searches. I planned to do a meta – analysis if the interventions, outcomes, and study methodology of the selected studies were similar and otherwise will perform a narrative assessment.

I found no randomized controlled trials (RCTs) that addressed tight versus loose glycemic control in diabetic surgical patients. Since I did not find this type of article, I used the only two observational cohort studies I found during the search. Cohort study quality was assessed using the following questions from the *Clinical Epidemiology: The Essentials (13).*

1. Are all members of the cohort at risk for developing the outcome?
2. Is there complete follow-up on all members?
3. Are all members of the cohort assessed for outcomes with the same intensity?
4. Are comparisons unbiased?

Additional quality criteria specific to this type of studies were considered. I included the following nine criteria because they addressed the information that the *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice* indicated as needed in evaluating the quality of a cohort study (14, 15). The criteria are detailed for each study in Table 5:

1. DM definition -- A specific glycemic threshold, use of glucose-lowering agents, or both to define diabetes.
2. DM surveillance --A protocol to detect DM describes the proportion of patients not identified in initial screening of patients for study.
3. Risk factor for postoperative infection ascertainment -- methods to determine risk factors were described and applied to study and control subjects alike.
4. Risk factor for postoperative infection reporting --reports all factors evaluated (not just those considered significant).
5. Outcomes definition --diagnostic criteria for all outcomes assessed were described.
6. Outcomes ascertainment -- methods to determine outcomes were described and similarly applied to patients with and without outcome of interest.
7. Outcomes blinding -- outcomes were assessed by investigators blind to diabetic status.

8. Outcomes reporting – outcomes obtained by the investigators were described.

9. Outcomes adjustment -- prognostic estimates were adjusted for differences between those with and without outcome of interest.

Quality criteria noted above were listed as present, not present or unable to be determined. This method was selected in order to assess the overall quality of each study based on factors that were major methodological components of a research study on this particular topic. In addition, Bradford-Hill criteria will be used to determine if there is evidence that an association also had a cause and effect relationship. These criteria are as follows (13):

1. Temporal relationships between cause and effect – Cause precedes effect.
2. Strength of Association – A strong association is expressed by a large measure of effect.
3. Dose-Response Relationships – Larger exposures to purported cause associated with higher rates of disease.
4. Reversibility – Reduction in exposure associated with lower risk of disease.
5. Consistency – Repeatedly observed by different persons, in different places, circumstances, and times
6. Biologic plausibility – Makes sense, according to biologic knowledge of the time.

Data abstracted from the studies by the reviewer was entered into evidence tables. This data included glucose levels in control and intervention groups, statistical significance of outcome differences between or among groups, and absolute and percentage change in perioperative outcomes in both the control and intervention groups. Estimates of effects with p-values or 95% confidence intervals (CIs), as appropriate, were recorded.

RESULTS

Study Identification

A total of 292 citations were identified in the computerized database search. The citations identified included 180 from Medline, 103 from CCTR and 9 from the CDSR, ACP Journal Club, and DARE databases combined. All 292 abstracts were reviewed. Studies unrelated to the objectives of this review were eliminated. Forty-one articles were subjected to full text review. An additional study, which was identified from reference lists, was also fully reviewed.

Forty-two studies meeting initial screening criteria received a more detailed evaluation. Thirty-nine studies were excluded for the following reasons: 8 were unrelated to glucose control, 9 assessed operative risks but not specific outcomes, 16 focused on management of diabetes during surgery but did not address glucose control with respect to outcomes, 2 addressed insulin protocols with no perioperative outcome evaluation, and 4 were retrospective.

Two included studies met the inclusion criteria for review. Neither study randomized patients into tight versus standard control or blindly assessed outcomes. The first study focused on perioperative nosocomial infection rates in diabetic patients undergoing elective surgery (16). The second study dealt with infectious complications among diabetics who had coronary artery bypass surgery (2). This study addressed three types of postoperative infections including wound infection (2). In the studies that were included, the control group received usual care, which was not further specified by the authors.

The two studies included used a prospective cohort design. One study also used the members in the cohort to develop a case control study (2). Based on these differences between the two studies, the heterogeneity of settings, perioperative outcomes, varying operation procedures and patient populations, I decided not to conduct a statistical meta-analysis pooling the results of studies. A narrative synthesis of this body of literature forms the next section of this paper.

Results of Studies

A Study Focusing on Multiple Sites of Infection

Golden et al examined the relationship between perioperative glycemic control and the subsequent risk of infectious complications, such as leg or chest wound infections, pneumonia, and urinary tract infections (UTIs) (Table 1). The researchers observed 411 adults with diabetes who underwent coronary artery surgery from 1990 to 1995 on the cardiac surgery service of an urban university hospital (2). Patients were chosen based on chart review, diabetic status verified from doctor's documentation, ER note, admission orders, nursing database or discharge summaries from previous hospital admissions (2).

This study compared two prospective cohorts against each other. The patients were followed from 36 hours post operatively and their baseline data was also collected. The researchers then gathered a second set of outcome data from postoperative day 2 until discharge to create a 48-hour lag between exposure and outcome.

Postoperative glycemic control was characterized by the mean of six capillary glucose measurements taken during the 36-hour interval following surgery. The major outcomes examined were infections of the leg and chest, pneumonia and urinary tract infections. In their analysis, the mean postoperative glucose levels were divided into quartiles: quartile 1 (121 – 206 mg/dL), quartile 2 (207 – 229 mg/dL), quartile 3 (230 – 252 mg/dL) and quartile 4 (253 – 352 mg/dL) (2).

The authors used these quartiles to compare postoperative outcomes for diabetic patients. The researchers compared the relative odds of infectious complications among patients in the second, third, and fourth quartiles with those in the first quartile. With this information, the researchers constructed a series of multiple logistic regression models (2). To determine the independent association between glycemic control and the risk of infection, the authors adjusted in quartiles for age, sex, race, Charlson Comorbidity Index, Acute Physiology and Chronic Health Evaluation (APACHE III) score, and length of stay in the surgical intensive care unit (2).

The Charlson Comorbidity Index tool for assessing the presence of comorbid conditions based on past medical history information found in the admission note and the problem list from the patients discharge summary in the index and their possible effects on the outcome were used by the researchers.

To assess the overall severity of illness, Golden et al used the APACHE III prognostic system. The APACHE III score is a predictor of in-hospital mortality in critically ill patients (2). The score is a function of the following variables: temperature, heart rate, mean blood pressure, respiratory rate, arterial pH, pulmonary carbon dioxide concentration (pCO2), pulmonary oxygen concentration (pO2), sodium, blood urea nitrogen, creatinine, glucose, leukocyte count, hemotocrit, total bilirubin, albumin, urine output, and neurological status (2).

After adjusting for confounders, the relative odds ratios for infection among individuals in quartiles 2, 3, and 4 were 1.17 (0.57 – 2.40), 1.86 (0.94-3.68), and 1.72 (0.86-3.47) respectively, in comparison to individuals in quartile 1(2). There was no dose response relationship with these odds ratios which argues against a clearly causal relationship. Additionally, these differences were not significant since the CIs for these relative odds ratios (RORs) all overlap 1.0.

The researchers wanted to exclude the possibility of a subclinical infection during the first 36 hours postoperatively, which could have accounted for findings of an increased infection risk. (2). Therefore, Golden et al performed a secondary analysis excluding individuals who developed infectious complications on postoperative day 2 (2). Nevertheless, a similar result was found after adjusting for all the confounders measured at the 36-hour time period.

The relative odds of infection among individuals in quartiles 2, 3 and 4 were somewhat higher with relative odds ratios and CI's as follows: (0.94 (0.39-2.26), 1.59 (0.71-3.54), and 1.78 (0.79-4.05)). Although there appeared to be a trend of increased infection risk with increased glucose levels, the CI's for each of these RORs again overlap1.0 such that these differences were not statistically significant. This lack of an association may be secondary to the relatively small sample size for each quartile or a true lack of association.

A Study Focused on Nosocomial Infections

Pomposelli et al examined prospectively the effects of glucose control on diabetic surgical patients with respect to nosocomial infection rates (Table 1). One hundred initially uninfected diabetic patients undergoing elective surgery were monitored for perioperative glycemic control and postoperative nosocomial infection rate. Three of these patients were excluded when preoperative infections were found. Serum blood glucose measurements were collected preoperatively and on postoperative day (POD) 1 and 2 for the remaining 97 patients (16). Patients were excluded from statistical analysis on days when no glucose determinations were available.

Preoperative patient characteristics and the type of operation performed were used to stratify outcomes. There were no significant differences between preoperative characteristics or operation types among patients with nosocomial infections versus those without. In performing the analysis, a serum glucose value of less than or equal to 220 mg/dL was considered to represent good glucose control. Patients were monitored for infection rates up to discharge or a maximum of 14 PODs for a prolonged hospitalization.

A single blood glucose value greater than 220 mg/dL on POD 1 was associated with an infection rate of 31.3%. The infection rate was 11.5% ($p<0.05$) when all of a patient's blood glucose levels were less than 220 mg/dL (Table 2) (16). The most common complications were leg wound infection (10.9%), urinary tract infections (6.6%), sternal wound infections (5.6%), and pneumonia (4.6%) (2).

Pomposelli et al also examined the affect of hyperglycemia on infection incidence. Patients who developed nosocomial infections on POD 1 were more likely to have a higher perioperative maximum and mean glucose levels than those who did not develop an infection. Moreover, when simple infections of the UTIs were excluded, hyperglycemia greater than 220 mg/dL was associated with a 5.8 fold increase in the nosocomial infection risk in comparison to patients with levels less than 220 mg/dl (24.6% vs. 4.2%, $p < 0.03$) (16). However, since the researchers did not mention the desire to analyze the data without including UTIs a priori, I was concerned that they were modifying the data in an attempt to obtain the result they desired.

QUALITY OF THE STUDIES

Quality of the Golden study

In the Golden study, all diabetic patients who had coronary bypass surgery at an urban hospital participated. The researchers adjusted for differences in the patient characteristics by using the Charlson Comorbidity Index and the APACHE III score. The patients in each group were equally likely to have had an infection identified by the inpatient health care team.

In determining the presence of infection, the health care team used the same methods to follow patients in both groups. There was complete follow up of all patients in the time period allocated for the study by the researchers. The study accurately assessed risk factor for postoperative infection ascertainment, risk factor for postoperative infection reporting, defining of outcomes, outcome ascertainment, outcome reporting and adjustment of the outcome data (Table 3).

This study was a cohort study which only allowed for an association between hyperglycemia and postoperative infection to be determined from the results. However, the results of the adjusted data were not statistically significant. Additionally, although temporality was shown with hyperglycemia appearing prior to the onset of an infection, other Bradford-Hill criteria were absent. The study did not show sufficient strength of association with RORs from 1.17-1.86. There also was no dose-response curve in the primary analysis with ROR values going from 1.17 up to 1.86 and then down to 1.72 by quartile.

However, a non- statistically significant dose response curve was present in the secondary analysis which controlled for infectious complications on POD 2. The lack of a statistically significant association between hyperglycemia and infection rates does not in itself support a valid association. However, even if an association was suggested by the data, I would have been unable to assign a causal relationship to hyperglycemia and postoperative infection since many of the Bradford-Hill criteria were absent.

Another limitation was that there was little information related to pre-existing diabetic microvascular disease, such as retinopathy, nephropathy and neuropathy. The authors indicated that it was impossible to determine whether poor perioperative control was simply indicative of poor long-term control and pre-existing microvascular disease. Second, it was possible that subclinical infection within 36 hours following surgery actually led to hyperglycemia.

Finally, this was an observational study in which the level of glycemic control was not assigned and physicians might have chosen tighter control for patients with perceived higher risk of infection or a higher risk of hyperglycemia (2). Additionally, there could have been patients with good control prior to entering the study. These patients are less likely to become infected and to have better postoperative outcomes.

The authors observed that the relationship of perioperative glycemic control to complication risk was independent of age and proteinuria and that comorbidity reduces the likelihood that this limitation influenced the results (2). The results of the lagged analysis suggested that the hyperglycemia was not the result of pre-existing subclinical infections (2). If physicians were more likely to choose tighter control in patients perceived to be at higher risk, the results could have been biased toward the null causing the true risk associated with hyperglycemia to be underestimated (2). Additionally, if the patients were already well controlled and perceived to be at lower risk, the physicians could have been more likely to choose less rigorous control in these patients. This could cause the risk to be overestimated in these patients.

Quality of the Pomposelli study

Pomposelli et al used groups with a similar risk of perioperative infection. Uninfected diabetic patients undergoing elective surgery were enrolled. Patients with evidence of a preoperative infection, who were immunocompromised, or who required hemodialysis were excluded to eliminate other characteristics that could have potentially increased a patient's infectious risk. The APACHE II score, a score predicting mortality in critically ill patients, was used to adjust for potential confounders during analysis.

The clinical team used this score to identify patients' nosocomial infection status. The researchers had complete information on all included patients from POD 2 to POD 14. This study accurately defined the diabetic population, determined risk factor for postoperative infection ascertainment, defined outcome ascertainment, reported outcome and adjusted outcome data for potential confounders (Table 3).

This also was a cohort study and so only a non-causal association can be determined from the results. Pomposelli et al showed a lower infection incidence of 11.5% when all of patient's blood glucose levels were less than 220 mg/dL. This result was statistically significant. However, the most impressive difference, a 5.8 fold increase in nosocomial infection risk, was seen in patients with blood glucose levels greater than 220mg/dL in comparison to those with levels less than 220mg/dL. However, this data was tabulated after UTI data was removed. This analysis is questionable since the researchers did not decide a priori to perform it.

The temporality of the presence of hyperglycemia prior to nosocomial infection was established. Some association between hyperglycemia and nosocomial infections was shown with patients with levels less than 220mg/dL. These patients were found to have a statistically significant lower infection risk (11.5%) in comparison to those with levels greater than 220 mg/dL (31.3%). However, the strength of this association was not clear because of the methods used by the researchers in obtaining some of their results. Moreover, there was no dose-response curve shown in this study nor was reversibility addressed.

Neither of these studies attempted to implement an "optimal control protocol". These studies are simple observations and as such much more likely not to lead to the determination of a causal link. Patients with good control will have better perioperative control and will be inherently less likely to have complications. It says almost nothing about their hospital care.

Studies Not Meeting Inclusion Criteria

Two studies that did not meet review criteria, but can help in understanding research in this field, were by Latham et al (17) and Furnary et al (18). Latham assessed the importance of diabetes, diabetes control, hyperglycemia, and previously undiagnosed diabetes in the development of surgical site infections among cardiothoracic surgery patients. Patients having coronary artery bypass or cardiac valvular procedures at Saint Thomas Heart Institute in Tennessee were followed prospectively to identify those who developed surgical site infections (SSIs) (17).

One thousand patients in the Latham study had HgA1c determinations performed preoperatively to determine their diabetic status. The normal values were determined to be between 4.2% and 6.2%. Thirty patients out of the initial one thousand were found to have surgical site infections (SSIs). Forty-four additional cardiothoracic surgery patients, not enrolled in the HgA1c evaluation, were also identified through routine surveillance as having developed SSIs. The seventy-four infected patients (thirty initial patients plus the forty-four added patients) were the cases and the nine hundred and seventy initially uninfected patients served as the controls when the researchers looked at the effects of hyperglycemia on SSI rates.

According to the Latham study, twenty-six (62%) of the forty-two patients with known diabetes with SSIs had hyperglycemia after surgery compared with one hundred and twenty three (44%) of two hundred and seventy eight diabetics without SSIs who did not (odds ratio [OR], 1.86; 95% confidence interval (CI 95), [1.04 – 3.34]; P=0.03) (17). The ORs of SSI s were 2.54, 2.97 and 3.32 among patients with postoperative glucose levels of 200 to 249, 250 to 299, and 300mg/dL or greater, respectively (compared to those with levels less than 200 mg/dL; P<0.0001) (17). Confidence intervals for Ors were not given in the paper (17).

Furnary et al conducted a study of tight glucose control using continuous intravenous insulin infusion (CII) compared to sliding scale guided intermittent subcutaneous insulin injections (SQI). Incidence of deep sternal wound infections (DSWI) in diabetic patients after cardiac surgical procedures was the primary outcome. The Portland CII protocol consisted of a starting intravenous insulin infusion dosage, frequent blood glucose testing, insulin infusion titration, and stopping orders.

In the Furnary study, all known diabetic patients consecutively admitted to Portland St. Vincent Medical Center for open heart surgical procedures between January 1987 and November 1997 were entered (n=2467) (18). Nine hundred and sixty-eight diabetic patients were operated on between January 1, 1987 and September 1, 1991 and placed in a group which received individualized sliding scale guided SQIs as the method of postoperative glucose regulation.

The remaining 1499 diabetic patients operated on between September 1991 and November 1997, were cared for using the CII protocol (Appendix 1) for glucose regulation. The SQI group was treated every four hours to keep blood sugar at or below 200mg/dL (18). The CII group had the insulin drip titrated on the basis of the most recent fingerstick glucose measurement to maintain blood glucose levels between 150 and 200 mg/dL (18).

Overall, 31 of the 2467 diabetic patients developed deep sternal wound infections (1.3%) (18). Daily comparison of mean blood glucose levels between the SQI and CII groups demonstrated tighter control in the CII group. Mean blood glucose levels on the day of operation through the third POD were significantly lower within the CII group than in the SQI group (199 $\pm$ 1.4 versus 241 $\pm$ 1.9 mg/dL on the day of operation, 176 $\pm$ 0.8 versus 206 $\pm$ 1.2 mg/dL on POD 1, 181 $\pm$ 1.2 versus 195 $\pm$ 1.3 mg/dL on POD 2, and 179 $\pm$ 1.5 versus 188 $\pm$ 1.4 mg/dL on POD 3, CII group versus SQI group, respectively; $p<0.0001$ for all comparisons) (18).

The implementation of the CII protocol resulted in a 2.5-fold decrease in the rate of DSWI compared with that for SQI (18). The rate of DSWI dropped from 1.9% (19 of 968) with SQI to 0.8% (12 of 1,499) with CII ($p = 0.011$) (18). The absolute difference between these two protocols was 1.1% (1.9-0.8). This means that approximately 100 patients need to be treated with the protocol to prevent one DSWI.

Quality of the Studies

Quality of the Latham study

The association between hyperglycemia and SSIs appeared to be significant with a dose-response curve present. However, this was a poorly done case-control study. The weakness in the study stems from the method the researchers used in selecting patients. The researchers admitted forty-four patients, not originally sent for HgA1c evaluation, after finding out they had SSIs. The authors appeared to be trying to increase the number of cases to make their data significant.

Quality of the Furnary Study

The SQI and CII groups were diabetics having the same type of surgical procedures performed by the same surgical team. The researchers adjusted for the baseline differences between groups when analyzing the outcome data. First, the researchers performed a descriptive analysis of all demographic and patient characteristic data. They then performed a multivariate analysis of all individual variables with a possible association with DSWI. They felt that both groups were equally as likely to have had their outcomes identified by the clinical team because all patients were closely monitored in the hospital.

A limitation of the Furnary study was that the patients were classified into sequential groups. One protocol used patients from 1987 – 1991, and another protocol used in patients from 1991 – 1997. Therefore, this was a historical cohort study conducted over consecutive admission periods. This approach could cause selection bias since the patients from the later years could have been healthier, come from a different referral base, or been treated more effectively secondary to temporal advances in medicine and surgery during that time.

Neither Latham nor Furnary addressed other prior health conditions besides the presence of diabetes in a patient's likelihood of developing infection. If the patient already had depressed immune system function secondary to previously uncontrolled health problems, he or she could be at higher risk of becoming infected. This would bias the researchers' estimates of infection rates because these patients were more likely to suffer from an infection. Therefore, the authors should have analyzed the data after taking other possible confounders (e.g. coexisting chronic diseases and likelihood of poor outcomes) into account.

SUMMARY OF RESULTS

The main question from the results of the studies presented is whether or not there is an association between hyperglycemia and postoperative infections. Golden et al found a non –statistically significant association between hyperglycemia and postoperative infectious complications. Pomposelli et al found a statistically significant and large difference with fewer patients (N=100). However, the analytic strategy is questionable. The evidence for an association between reduced blood glucose levels and fewer postoperative infections from the included studies was weak.

Latham et al was a poorly done case control study where the researchers added cases at the end of a cohort study. In this study, the researchers showed that glycemic control made a difference in infection rates in wound and other study sites. The method used by the researchers when they conducted this study makes the evidence acquired from it poor. Furnary et al found a small difference (NNT = 100) with a historical cohort.

A historical cohort study is one where patients are identified from past records and followed forward from that time up to the present (13). This study design often produces data that may not be of sufficient quality for rigorous research (13). Therefore, this study design and the lack of an appropriate control group made the evidence for an association between hyperglycemia and DSWIs fair.

Another limitation of these studies was that blinding was not a part of the research process. This process could have taken place at four levels in the clinical trial. First, those responsible for allocating patients to treatment groups should not know which treatment will be assigned next so that the knowledge does not affect their willingness to enter patients in the trial or take them in the order they arrived (13). Second, patients should be unaware of whether they are in the treatment group or the control group; they are thereby less likely to change their compliance or their reporting of symptoms because of this information (13).

Third, the physicians who take care of patients in the study should not know which treatment each patient has been given; such that they will not, perhaps even unconsciously, manage them differently (13). Finally, it the researchers who assess outcomes cannot be allowed to distinguish treatment groups; that knowledge cannot affect their measurements (13). If blinding were incorporated into a study, the internal validity of the study can be maintained and the conclusion that could be inferred from the data would be stronger.

DISCUSSION

There have been no RCTs that addressed reducing postoperative infections in diabetic surgical patients. In the two included cohort studies, the case control study and the historical cohort study showed weak evidence that postoperative infections can be reduced with tighter perioperative glycemic control. My personal assessment of the results was that overall evidence was weak, but leaning in a positive direction. If better perioperative control might lead to fewer postoperative infections they why should we not strive for it? Are there potential consequences for obtaining better control? The implementation of "weak" evidence is controversial.

The included studies did not address adverse events that could result from this type of action. For example, would implementing this evidence waste resources on ineffective treatment? A significant amount of time and money would have to be used to implement a protocol for better glucose control. Nurses and other health care workers would have to increase monitoring of diabetic patients on the wards. This means the patients would have to endure more blood glucose checks and insulin injections.

Additionally, due to the increase in the administration of insulin, there is greater possibility of hypoglycemic episodes thus, increasing morbidity and/or mortality on diabetic patients. With the current evidence that exists at the present, it might be too much work for the little benefit that can be gained from implementing this protocol.

I wish there were RCTs available so that a cause and effect relationship could have been developed and reversibility could have been established between hyperglycemia and postoperative infections. The lack of a RCT in this area was a major problem in addressing this issue. Cohort studies do not allow for general recommendations for the management of diabetic patients undergoing surgical procedures to be given.

However, some recommendations can be given for taking care of individual diabetic patients. The results suggested that blood glucose levels of approximately 250 mg/dL or lower appeared to be associated with decreased infection incidence in diabetic patients. Therefore, if a physician is seeing a patient who is planning to undergo a surgical procedure, one might want to attempt to lower his or her blood glucose to 250 mg/dL or lower.

Unfortunately, beyond recommendations for the care of an individual patient, no guidelines can be made for the general population until causation is established between hyperglycemia and postoperative infections.

Association is not causation and association is all that can be drawn from cohort studies. Had the studies met the Bradford-Hill criteria, then I could say that the association between hyperglycemia and postoperative infection was causal. Although all the studies showed temporality and some showed a dose-response curve, many of the Bradford-Hill criteria were not met. Reversibility could not be shown in any of the studies due to their designs.

Consistency was not observed since the different studies obtained different results in their diabetic patients. In the Golden et al study, even if the results had been statistically significant, the researchers only found a small difference in infection between the quartiles (2). In contrast, Pomposelli et al found a statistically significant and large difference. Biologic plausibility has not conclusively been established on whether or not diabetics have an increased risk of infection in comparison to patients without diabetes (19). There is also no conclusive evidence that hyperglycemia causes diabetics to have an increased risk of postoperative infection.

Limitations of the Review

No randomized controlled trials were identified in the systematic literature search. There were only two prospective cohort studies found during this search. The lack of studies may be due to negative articles not being published (14).

Finding a limited amount of evidence related to my study question made it difficult to fully determine the role of tight glucose control on perioperative outcomes in diabetic patients. Without randomized controlled trials, the apparent relationship between the perioperative infections outcomes and glycemic control could not be fully determined. Another limitation is that only one reviewer evaluated the studies for inclusion, data abstraction and quality assessment. Ideally, several reviewers should be involved with formal testing of inter-rater reliability (14).

CONCLUSION

Practice Implications

Clinically, I am not sure that there is an association between hyperglycemia and postoperative infection incidence in diabetic surgical patients. There is a weak suggested association according to the evidence provided here, but it is far from clear. Some groups have already made recommendations (3, 4, and 5); however, there is little evidence to back them.

The evidence available at present makes it impossible to issue practice guidelines for the medical community to follow. However, I feel the evidence may be strong enough to make recommendations on an individual patient level. If a physician is seeing a patient, he or she might attempt to lower the patient's blood glucose as much as possible since the benefits would likely outweigh the potential risks to the patient.

Suggestions for Further Research

It would be helpful to have more research into the possible relationship between hyperglycemia and postoperative infection. The ideal research would be to have a randomized control trial so that a cause and effect relationship could be established.

However, conducting such a study would have many ethical implications. Placing patients into categories of "good" versus "bad" control would be difficult. However, a study looking at tight control versus standard care would be perfectly ethical. This is particularly true given the uncertainty about whether tight perioperative control improves outcomes or simply results in increased costs and morbidity (16).

Outside of the needed RCT there are several studies which could be done with existing data. One suggestion could be to look at the data from the UKPDS study and collect chart data from the participants who had surgeries. Then, for those patients, find out how many had tight or loose control of their blood glucose levels at that time of their operation and look at the infection rate between the two groups. The advantage to this type of study is that the preoperative records are more likely to be good and it would be relatively easy to obtain this data from the patients who participated in the study. However, there could be too few patients who had surgery during the time frame of the study or surgical outcomes may not have been collected uniformly.

Another idea would be to look at cross-sections hospitals that are aggressive in controlling glucose levels in their surgical patients versus those that are not as aggressive and compare infection rates between the institutions. This type of study could assist in addressing whether or not aggressive control makes a difference in postoperative infection rates. Additionally, it would allow possible adverse outcomes from better glycemic control to be addressed through hypoglycemic episode recording and nursing log data. However, it would be difficult to compare different hospitals in different locations, different patient populations and different perioperative glycemic control protocols.

Moreover, a time series study could be conducted in other countries. In a time series study, the effect is measured at various points in time before and after the purported cause has been introduced (13). If changes in the purported cause are followed by changes in the purported effect, the association is less likely to be spurious (13). An example of this would be to go to another area (e.g. India or Africa) that has no protocol in place for managing diabetic surgical patients. Then, begin a tight perioperative control protocol that is used in the U.S. The infection rates five years after beginning this protocol could be compared to infection rates from five years prior to the protocol's inception to see what, if any, difference tight perioperative control made in the infection rate in these countries.

This type of study would allow the effect of a particular protocol on infection rate to be established. There would be no issue of varying perioperative glycemic control protocols, because all hospitals would use the protocol given to them by the researchers. However, there would be some temporal bias since a comparison would be made between data from two different time points.

These suggestions could be implemented with both financial and organizational planning. However, due to the many flaws that are associated with these types of study designs, the only conclusive method of determining a causal relationship between hyperglycemia and postoperative infection would be to conduct a RCT. Therefore, future research should be directed into having a RCT conducted in this area. Only this type of study will afford the answer to the question posed in this paper. Since, the number of patients that will suffer from this disease in the future is continuing to rise, it is imperative that this type of research be conducted.

TABLES

Table 1:

Two Studies with Diabetic Patients with Other Infectious Outcomes

Citation	Study design and patient population (total N)	Outcomes	Perioperative outcome present	Perioperative outcome absent	OR or RR (95% CI)	P value
Golden et al 1999 (2)	Cohort Study: Patients were followed to compare infection incidence in patient with lower glucose levels (Quartile 1)* to those with higher levels (Quartiles 2-4)* (N=411)	Leg and chest wounds, pneumonia, and UTIs	Quartile 1: 21/104 Quartile 2: 22/102 Quartile 3: 31/104 Quartile 4: 26/101	Quartile 1: 83/104 Quartile 2: 80/102 Quartile 3: 73/104 Quartile 4: 75/101	Quartile 1: OR 1:00 Quartile 2: OR: 0.94 (0.39-2.26) Quartile 3: OR: 1.59 (0.71-3.54) Quartile 4: 1.78(0.79-4.05)	
Pomposelli et al 1998 (13)	Prospective cohort study: Diabetic patients undergoing elective surgery were monitored for perioperative glucose control and nosocomial infection (N =97)	Nosocomial infection	≤220 mg/dl: 1/24 (4.2%) > 220 mg/dl: 15/61 (24.6%)	≤220mg/dl : 23/24 (95.8%) >220 mg/dl: 46/61 (75.4%)	NA NA	0.03

Quartile 1: blood glucose levels: 121-206 mg/dL. Quartile 2: 207-229 mg/dL. Quartile 3: 230-252 mg/dL. Quartile 4: 253-352 mg/dL.

Table 2:

Blood Glucose and Infection Rate Contingency Tables for Each Study Day (Pomposelli et al 1998) (16)

	Highest glucose (mg/dl)	Became infected	Remained uninfected	Total	Infection rate (%)	P value
A:	<220	15	47	62	24.2	0.87
Preop	>220	9	26	35	25.7	
	Total	24	73	97	24.7	
B:	<220	3	23	26	11.5	0.05
POD 1	>220	21	46	67	31.3	
	Total	24	69	93	25.8	
C:	<220	9	30	39	23.0	0.63
POD 2	>220	14	37	51	27.5	
	Total	23	67	90	25.6	

Table 3:

Quality of Included Studies

Study number	1. DM Definition	2. DM Surveillance	3. RF Ascertain-ment	4. RF Reporting	5. OC Definition	6. OC Ascertain-ment	7. OC Blinding	8. OC Reporting	9. OC Adjust-ment
1. Golden (7)	-	-	+	+	+	+	-	+	+
2. Pomposelli (13)	+	-	+	+	+	+	-	+	+

1. DM definition - a specified glycemic threshold, use of glucose-lowering agents, or both were used to define diabetes;
2. DM Surveillance - a protocol to detect DM was described the proportion of patients not identified in initial screening of patients for study;
3. Risk factor for postoperative infection ascertainment - methods to determine risk factors were described and similarly applied to study subjects and control subjects;
4. Risk factor for postoperative infection reporting - all factors evaluated (not just those that were significant) were reported;
5. Outcomes definition - diagnostic criteria for all outcomes assessed were described;
6. Outcomes ascertainment - methods to determine the outcomes were described and similarly applied to patients with and without infection;
7. Outcomes blinding - outcomes were assessed by investigators blind to diabetes status;
8. Outcomes reporting – outcomes obtained by the investigators were described;
9. Outcomes adjustment - prognostic estimates were adjusted for differences between those with and without infection;

+, study met my review's methodological study criterion; -, study did not meet my review's methodological quality criterion. (Model for this table was adapted from Montori VM et al. Posttransplantation Diabetes: A Systematic Review of the Literature. *Diabetes Care,* Volume 25, number 3, March 2002.)

APPENDIX

Appendix 1:

Portland Protocol for Continuous Intravenous Insulin Infusion in Postoperative Diabetic Patients Undergoing Cardiac Surgical Procedures (Furnary et al 1999) (21)

1. Start insulin infusion through pump piggyback to maintenance intravenous infusion as follows: Test blood glucose level by fingerstick method or arterial line drop sample:

Blood Glucose (mg/dL)	Insulin (units/h)
< 150	0
150 – 200	1
201 – 250	2
>251	3

2. Frequency of blood glucose testing:

a. Every hour until stable (when frequent changes in insulin dosage are no longer necessary, and glucose is in the range 150 to 200 mg/dL); then test every 2 hours.
b. When weaning from vasopressors (e.g., epinephrine), check every 30 minutes until stable.
c. May stop testing every 2 hours on postoperative day 3 [see item 4].

3. Insulin titration:

Blood Glucose	Action
<75	Stop insulin; give 25 mL of 50% dextrose injection and recheck blood glucose in 30 min; when blood glucose is >150 mg/dL, restart with rate 50% of previous rate
75-100	Stop insulin; recheck blood glucose in 30 min,

	when blood glucose is >150 mg/dL, restart with rate 50% of previous rate
101-150	If <10% lower than last test, decrease rate by 0.5 units/h; if >10% lower than last test, decrease rate by 50%
151-200	Same rate
201-250	If lower than last test, use same rate; if higher than last test, increase the rate by 0.5 units/h
>250	If > 10% lower than the last test, use same rate; if <10% lower than last test, increase rate by 1 unit/h

If blood glucose is >251 mg/dL and has not decreased after three hourly increases in insulin, then double insulin rate.

4. Start continuous intravenous insulin protocol during operation and continue postoperatively through the day of operation and continue postoperatively through the day of operation and the first and second postoperative days. Patients who are not receiving enteral nutrition on the third postoperative day should remain on this protocol until receiving at least a soft American Diabetes Association diet.

5. American Diabetes Association diabetic diet starts with any oral intake.

6. On the third postoperative day, restart preadmission glycemic control medications when patient is tolerating soft diet. If not tolerating soft diet, consult physician for new orders at that time.

7. For patients with previously undiagnosed diabetes mellitus and hyperglycemia: start Portland protocol if blood glucose is > 200 mg/dL. Consult endocrinologist on postoperative 2 for diabetes mellitus workup and follow-up orders.

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